Effects of *N*-acetylcysteine on renal dysfunction in neonates undergoing the arterial switch operation

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Objective: We evaluated *N*-acetylcysteine, a potent antioxidant, as prevention for renal dysfunction in infants undergoing cardiac surgery for dextro-transposition of the great arteries.

Methods: Twenty-one neonates undergoing the arterial switch operation were randomized to receive either placebo or intravenous *N*-acetylcysteine. Serial data were collected on fluid balance, serum creatinine, inotropic support, cardiac output, and length of stay.

Results: Hospital and 30-day survival was 100%. No serious adverse events were attributable to the drug. Subjects treated with *N*-acetylcysteine had a higher urine output at 24 hours (175 mL vs 96 mL; $P < .01$) and a shorter median time to first negative fluid balance (27 hours vs 39.5 hours; $P = .02$). There were no differences between groups in diuretic therapy, inotropic support, fluid intake, or chest tube output. Serum creatinine increased at 24 hours after the operation by a mean of 0.27 mg/dL with placebo ($P < .01$) but was unchanged with *N*-acetylcysteine treatment. By postoperative day 3, serum creatinine increased by 92% in the placebo group but only 38% in the *N*-acetylcysteine group ($P = .04$). Length of intensive care unit stay was shorter by an average of 5 days ($P = .04$) with *N*-acetylcysteine treatment.

Conclusions: In this pilot study, perioperative treatment with *N*-acetylcysteine resulted in improved urine output, shorter time to negative fluid balance, and attenuation of the rise in creatinine. These effects of *N*-acetylcysteine may translate to improved outcomes for infants undergoing complex cardiac operations. (J Thorac Cardiovasc Surg 2010;139:956-61)

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Cardiac surgery requiring cardiopulmonary bypass (CPB) is accompanied by varying degrees of ischemia–reperfusion injury to multiple organs including the heart, lungs, brain, liver, and kidneys. Multiorgan dysfunction contributes to longer postoperative recovery times and increased morbidity and mortality in adults and children undergoing surgical correction of major structural cardiac abnormalities.[1-3] Acute kidney injury is associated with significant morbidity and mortality after cardiac surgery in both adults and children.[4-6] Although the precise mechanisms for renal injury after bypass are incompletely understood, oxidant stress has been suggested to play a major role.

N-acetylcysteine (NAC), a derivative of the naturally occurring amino acid *L*-cysteine, has been used prophylactically to attenuate renal injury after intravenous contrast for radiologic studies. The beneficial effect of NAC is thought to be mediated by multiple mechanisms including free radical scavenging, prevention of oxidative stress, limitation of ischemia–reperfusion injury, and modulation of apoptosis.[7]

Multiple large, randomized, placebo-controlled trials have examined the role of NAC in the prevention of acute kidney injury in adults, but not children, after CPB.[8-12] Although none of these trials showed a clear benefit of NAC in the reduction of renal injury, two studies focusing on patients with pre-existing chronic renal insufficiency demonstrated significant benefits of NAC in reducing the duration of mechanical ventilation, length of intensive care unit stay,[11] and all-cause mortality.[12]

No previous studies have been published on the potential renal protective effects of prophylactic NAC in infants undergoing cardiac surgery. Compared with the adult kidney, the neonatal kidney is uniquely susceptible to ischemia–reperfusion injury after CPB.[13] In addition to the increased susceptibility to ischemia–reperfusion injury, the clinical outcome of infants with acute renal failure after surgery for congenital heart disease is known to be significantly worse, with an adjusted mortality odds ratio of 1.91 (95% confidence interval 1.10–3.36).[6]

We hypothesized that prophylactic NAC would preserve renal function after cardiac surgery in infants with complex congenital heart disease. We chose to study the efficacy of NAC in patients undergoing the arterial switch operation

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Abbreviations and Acronyms
ASO = arterial switch operation
CPB = cardiopulmonary bypass
D-TGA = dextro-transposition of the great arteries
NAC = *N*-acetylcysteine

(ASO) for dextro-transposition of the great arteries (D-TGA) because this operation is performed almost exclusively in neonates, requires CPB, and is known to produce a predictable fall in cardiac output reaching a nadir between 8 and 12 hours after surgery.[14] Mortality after ASO in the modern era is quite low (<5%), but significant secondary morbidity remains, including low cardiac output syndrome, postoperative fluid overload, and acute renal dysfunction, with a requirement for renal replacement therapy in 5% to 8% of cases.[15,16]

METHODS

This study was a randomized, placebo-controlled, double-blind trial of intravenous NAC in neonates and infants with D-TGA and variants (including D-TGA, ventricular septal defect, with/without aortic coarctation, and double-outlet right ventricle, subpulmonary ventricular septal defect, with/without aortic coarctation) undergoing ASO (with/without ventricular septal defect closure and aortic arch repair). Exclusion criteria included patients younger than 36 weeks' postconceptional age at the time of surgery, patients with a birth weight less than 1800 g, and patients with clinical or laboratory evidence of significant preoperative renal, hepatic, or neurologic dysfunction. Informed consent was obtained from the parents or legal guardians of all eligible patients. The study was approved by the University of Michigan Human Subjects Institutional Review Board. Funding agencies played no role in data interpretation.

Subjects were randomized to receive an intravenous bolus of NAC (100 mg/kg in 5% dextrose) or placebo (5% dextrose) 1 hour before the operation, followed by an intravenous infusion of NAC (10 mg $\cdot$ $kg^{-1} \cdot h^{-1}$) or an equal volume of placebo continuously for 24 hours after separation from CPB. A thermodilution cardiac output catheter was positioned in the main pulmonary artery during the operation whenever technically feasible. All four surgeons who performed the ASO during the study period standardized their intraoperative approach, including cooling rates and temperatures, cardioplegia administration, and cannulation techniques. At the conclusion of the operation, all patients underwent modified ultrafiltration.

Total fluid intake, urine output, and chest tube output were recorded hourly per our standard cardiac intensive care unit guidelines. Blood pressure, thermodilution cardiac output, central venous pressure, left atrial pressure, and vasoactive inotrope score were recorded at 1, 4, 8, 12, and 24 postoperative hours. Vasoactive inotrope score was defined as follows: dopamine ($\mu g \cdot kg^{-1} \cdot min^{-1}$) + dobutamine ($\mu g \cdot kg^{-1} \cdot min^{-1}$) + 100 × epinephrine ($\mu g \cdot kg^{-1} \cdot min^{-1}$) + 100 × norepinephrine ($\mu g \cdot kg^{-1} \cdot min^{-1}$) + 10 × milrinone ($\mu g \cdot kg^{-1} \cdot min^{-1}$) + 10,000 × vasopressin (units $\cdot$ $kg^{-1} \cdot min^{-1}$). Serial blood lactate levels were measured with each arterial blood gas (typically at 2- to 4-hour intervals over the first 24-hour period). Serum creatinine was measured preoperatively and at 1, 8, 24, 36 to 48, and 60 to 72 hours postoperatively. Postoperative mechanical ventilation time and postoperative intensive care unit and hospital lengths of stay were recorded (rounded to the nearest whole day). Complications and adverse events were recorded for all subjects.

Statistical Analysis

The primary outcome measure was the change in serum creatinine from preoperative (baseline) to 24 hours postoperative. Baseline data are represented as means with standard deviations or medians with ranges for nonnormally distributed values. The paired *t* test was used to test for within-subject changes in serum creatinine over time. The 2-sample unpaired *t* test was used to compare mean differences in fluid input/output and hemodynamic parameters between groups. To account for the nonindependence of the repeated measures over time, we used generalized estimating equations to test differences in serum creatinine over time between the treatment and placebo groups. The 2-sample Wilcoxon rank sum test was used to compare differences in time to negative fluid balance between groups, and a Kruskal–Wallis equality-of-populations rank test was used to compare other nonnormally distributed data such as length of stay between groups.

RESULTS

Between April 2005 and June 2008, 21 patients undergoing ASO were enrolled in the study. Two enrolled subjects were removed from further analysis because a pulmonary artery band was placed before ASO in 1 placebo-treated patient and extracorporeal membrane oxygenation was initiated before administration of the maintenance infusion of NAC in the second. Both patients were considered protocol violations. Therefore, the study sample available for analysis consisted of 9 placebo-treated and 10 NAC-treated subjects.

Baseline demographics were similar between the 2 groups (Table 1), and hospital as well as 30-day survival was 100% overall.

In the placebo-treated group, serum creatinine increased significantly compared with preoperative levels in the 24 hours after ASO (mean ± standard deviation, 0.56 ± 0.19 mg/dL vs 0.83 ± 0.19 mg/dL; $P = .0016$). An increase was observed in all 9 placebo subjects at this time point. In contrast, serum creatinine was not statistically different between preoperative and 24-hour postoperative measurements in the NAC group (0.57 ± 0.22 mg/dL vs 0.66 ± 0.16 mg/dL; $P = .12$). In 4 of 10 subjects, serum creatinine either stayed the same or decreased at 24 hours compared with preoperative levels (Figure 1, *A*). A 2-sample *t* test showed a significant difference in the relative change in creatinine over this period between the 2 groups ($P = .030$).

In the placebo-treated group, serum creatinine also increased significantly in the first 3 days after ASO (mean ± standard deviation, 0.56 ± 0.19 mg/dL vs 0.99 ± 0.44 mg/dL; $P = .015$). In the NAC group, there was a significantly smaller rise in serum creatinine over this time period (0.57 ± 0.22 mg/dL vs 0.74 ± 0.24 mg/dL; $P = .012$; Figure 1, *B*). The relative rise in serum creatinine at 3 days postoperatively was attenuated by 60% in the NAC-treated patients compared with the placebo group (Figure 2).

Subjects who received NAC had a 1.8-fold increase in cumulative urine output over the first 24 postoperative hours compared with the placebo group (mean ± standard deviation, 176 ± 55 mL vs 96 ± 54 mL; $P = .0059$; Figure 3), despite no clinically meaningful changes in either total fluid

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TABLE 1. Baseline characteristics of the study population

	Placebo	NAC	*P* value
N	9	10	—
Mean birth weight (kg)	3.14	3.34	.33
Mean age at surgery (d)	7	6.9	.93
Mean postconceptional age at surgery (wk)	39	40	.075
Male gender (n)	4	8	.36
Balloon septostomy (n)	4	6	1.0
Noncardiac anomalies (n)	0	1	1.0
Mean serum creatinine (mg/dL)	0.56	0.57	.71
D-TGA with IVS (n)	5	7	1.0
D-TGA with ventricular septal defect (n)	2	3	1.0
DORV with subpulmonary VSD (n)	2	1	.56
Coarctation of the aorta, repair done with DHCA (n)	4	1	.12
Intramural coronary course noted by preoperative echocardiogram (n)	1	4	.32
CPB time (min)	184	161	.36
Crossclamp time (min)	98	85	.53

D-TGA, Dextro-transposition of the great arteries; *IVS*, intact ventricular septum; *VSD*, ventricular septal defect; *DORV*, double-outlet right ventricle; *CPB*, cardiopulmonary bypass.

intake (669 ± 159 mL vs 626 ± 235 mL; $P = .64$) or chest tube output (135 ± 102 mL vs 153 ± 127 mL; $P = .73$). This enhanced urinary response in the NAC group resulted in earlier time to a negative fluid balance (defined as the first consecutive 6-hour period in which urine output was greater than fluid intake) compared with the placebo-treated patients (median, 27.0 hours vs 39.5 hours; $P = .022$; Figure 4).

With the exception of a slightly higher average chlorothiazide dose in the placebo group at postoperative day 3, there were no statistically significant differences in hemodynamic parameters, cardiac output, serum lactate, inotropic support, or diuretic therapy between the 2 study groups (Table 2).

Peritoneal dialysis was required in 2 of 9 placebo-treated patients and in no patients in the NAC group. No subjects in either group had end-stage renal disease. On the basis of the Acute Kidney Injury Network criteria,[17] 8 of 9 patients in the placebo group sustained acute kidney injury compared with 4 of 10 in the NAC group, with an odds ratio for acute kidney injury after NAC treatment of 0.08 (exact 95% confidence interval, 0.002–1.21; Fisher's exact test $P = .057$).

Intensive care unit length of stay was shorter by an average of 5 days in the NAC group versus the placebo group (6 vs 11 days; $P = .041$). Although not statistically significant, shorter average days requiring mechanical ventilator support and hospital length of stay for the NAC group compared with the placebo group were observed (median, 4.5 vs 7 days with ventilatory support, $P = .12$; 14 vs 16 days in hospital, $P = .25$, respectively).

No adverse events were directly attributable to NAC administration, and no statistically significant differences were observed between groups in the frequency of any adverse event (Table 3). During the 24-hour study period, serial cardiac output was measured by thermodilution via a 4F thermodilution catheter inserted through a 4F femoral venous sheath; this resulted in transient, reversible lower extremity venous congestion in 3 subjects. Early (within 30 days)

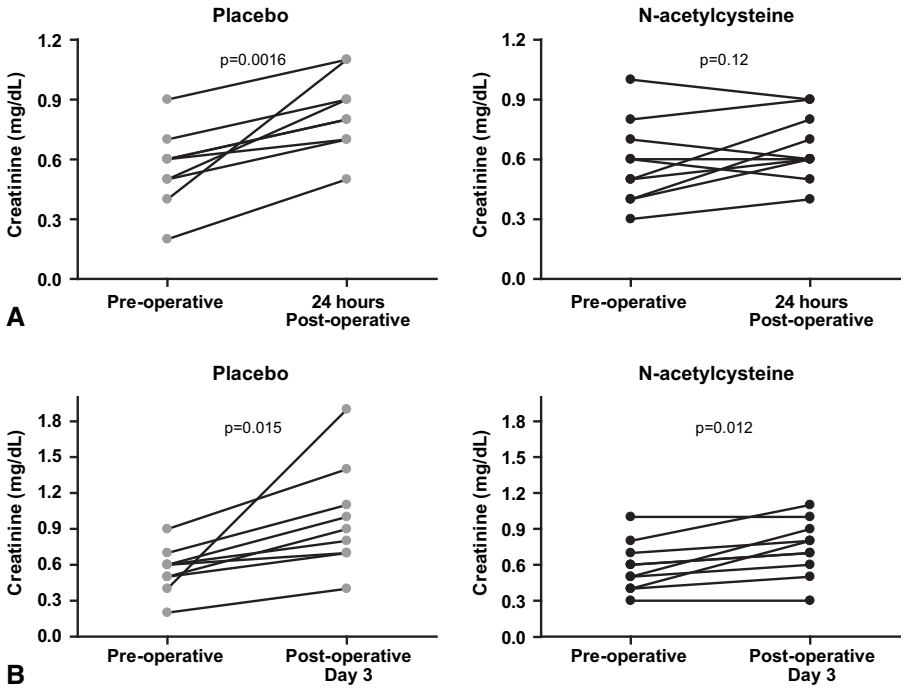

FIGURE 1. Serum creatinine before surgery and 24 hours postoperatively (A) and before surgery and on postoperative day 3 (B), by group. Serum creatinine is shown for each subject at these 2 time points, with the *connecting line* indicating the trajectory for each subject. Each *P* value is calculated by a paired *t* test.

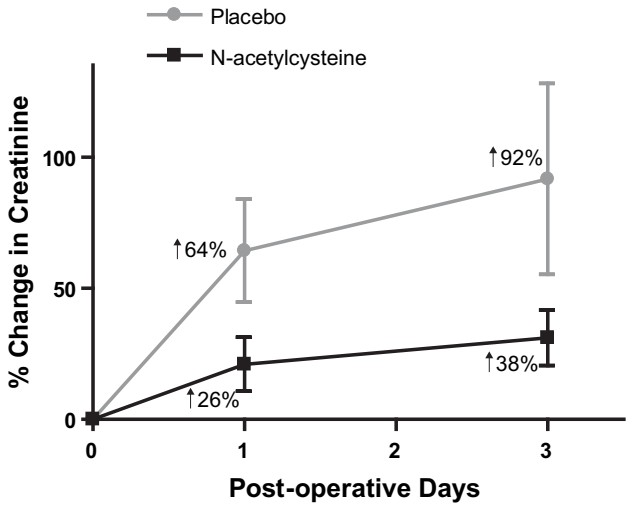

FIGURE 2. Postoperative change in serum creatinine by group. Percent change in mean serum creatinine from baseline is shown for placebo *(gray line)* and *N*-acetylcysteine–treated *(black line)* subjects. *Error bars* represent standard error of the mean.

cardiac reoperation was required in 1 patient owing to residual right ventricular outflow tract obstruction. Early catheter-based intervention was required in 1 patient to occlude a large aortopulmonary collateral vessel. Three of 20 subjects required early re-exploration for bleeding, with no difference between NAC and placebo groups. Arrhythmias requiring treatment occurred in 8 subjects, with supraventricular tachycardia in 3 patients, junctional ectopic tachycardia in 4 patients, and transient complete heart block in 1 patient.

DISCUSSION

This pilot study provides preliminary evidence in support of our hypothesis that NAC treatment is safe and attenuates postoperative acute renal injury in neonates undergoing cardiac surgery. The results were promising for NAC treatment, whether assessed by serum creatinine, urine output, or the Acute Kidney Injury Network consensus criteria. Compared with placebo-treated subjects, NAC-treated subjects had, on average, improved urine output by nearly 2-fold over the first postoperative 24 hours, an attenuated rise in postoperative serum creatinine over the first postoperative 72 hours, and a shorter average time to a negative fluid balance. This study was not powered to detect differences in mechanical ventilator time, intensive care unit length of stay, or hospital length of stay, but all 3 outcome measures were shorter for NAC-treated patients than for placebo-treated subjects.

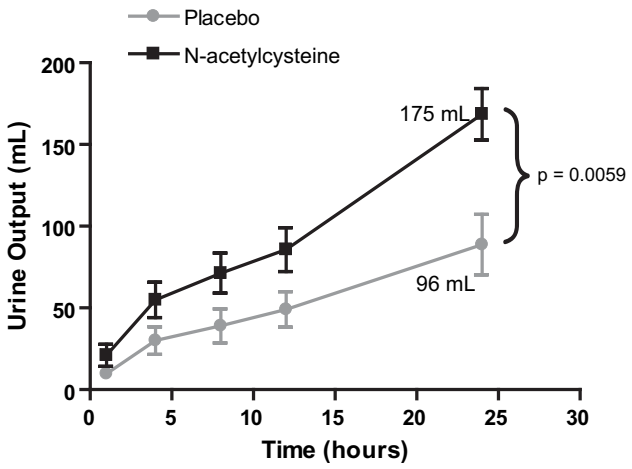

FIGURE 3. Cumulative urine output over postoperative 24hours by group. Total urine output (in milliliters) is shown for placebo *(gray line)* and *N*-acetylcysteine–treated *(black line)* subjects. The *P* value is calculated from a 2-sample unpaired *t* test. *Error bars* represent standard error of the mean.

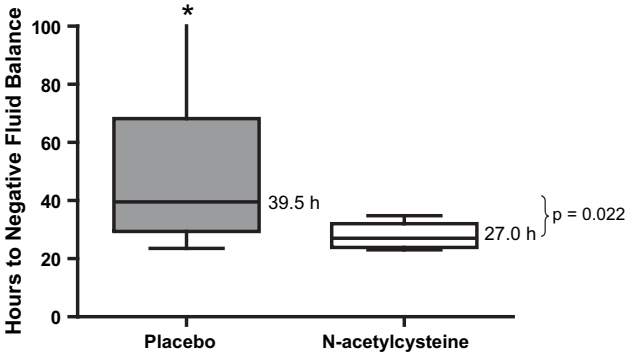

FIGURE 4. Time to negative fluid balance by group. The median time to achieving a negative fluid balance, defined as a 6-hour period during which urine output is greater than total fluid input, is shown for placebo and *N*-acetylcysteine–treated patients. *P* is calculated from a 2-sample Wilcoxon rank sum test. *Error bars* represent minimum and maximum values. *Single outlier at 211.2 hours.

Serial cardiac output was measured by thermodilution because of the possibility that postoperative low cardiac output, which is known to occur after ASO,[14] may have been abrogated by NAC. Previously, we showed that NAC treatment of isolated, perfused rabbit kit hearts significantly attenuated left ventricular dysfunction after 90 minutes of hypothermic ischemic arrest and reperfusion (J. Charpie, unpublished data). Owing to the technical difficulties and variability of thermodilution cardiac output measurements in neonates, a much larger sample size will be required to answer this important question.

NAC likely exerts its protective activity on the kidney through at least 2 principal mechanisms, including (1) an increased supply of intracellular reduced glutathione resulting in enhanced activity of superoxide dismutase and glutathione peroxidase, as well as improved oxygen-derived free radical scavenging,[18,19] and (2) inhibition of the intrinsic pathway of apoptosis induction.[20] We did not attempt to elucidate the mechanism of the protective effect of NAC in this study, and further study is warranted.

These results stand in contrast with the recent adult literature, where a large meta-analysis of 12 studies showed no consistent benefit of NAC in attenuating renal dysfunction in adult cardiac surgical patients.[21] We believe that this

TABLE 2. Hemodynamic data, cardiac output, vasoactive inotrope score, serum lactate, fluid balance, and diuretic requirement by group

Parameter	Placebo (n = 9)	NAC (n = 10)	*P* value
Mean arterial pressure (mm Hg)			
1 hour postop	59	56	.54
8 hours postop	49	54	.32
12 hours postop	51	53	.65
Mean cardiac index* ($L \cdot min^{-1} \cdot m^{-2}$)			
1 hour postop	2.5	2.6	.73
8 hours postop	2.0	2.4	.39
12 hours postop	2.2	2.8	.25
Mean VIS			
1 hour postop	12.3	10.7	.43
8 hours postop	19.3	17.5	.43
12 hours postop	21.5	18.4	.18
Maximum VIS during first 24 postop hours	23.0	20.5	.28
Mean serum lactate (mmol/L)			
Maximum VIS during first 24 postop hours	4.6	4.0	.54
Mean fluid input/output during first 24 postop hours			
Total fluid input (mL)	626	669	.64
Total fluid output (mL)	249	310	.23
Chest tube output (mL)	153	135	.73
Urine output (mL)	96	175	.0059
Diuretic requirements ($mg \cdot kg^{-1} \cdot d^{-1}$)			
Postop day 1 furosemide	4.2	3.8	.094
Postop day 1 chlorothiazide	6.7	5.3	.74
Postop day 2 furosemide	6.3	6.2	.98
Postop day 2 chlorothiazide	20.1	17.9	.057
Postop day 3 furosemide	7.4	6.8	.75
Postop day 3 chlorothiazide	20.4	17.4	

NAC, N-acetylcysteine; *VIS,* vasoactive inotropic score. *Data collected in a subset of 13 subjects (5 placebo and 8 NAC).

TABLE 3. Adverse events by group

	Placebo (n = 9)	NAC (n = 10)	*P* value
Bleeding, chest tube for hemothorax	0	1	1
Bleeding, early re-exploration required	2	1	.58
Early cardiac reoperation or catheter-based intervention	2	0	.21
Arrhythmia necessitating treatment	2	6	.17
Infection necessitating treatment	4	2	.35

NAC, N-acetylcysteine.

difference arises from several factors. First, our study was limited to neonates with a single, well-defined structural congenital heart defect and no significant comorbidities. In contrast, the adult studies included patients with multiple cardiac abnormalities, particularly coronary artery disease, and several coexisting risk factors for end-organ dysfunction. Second, our patients sustained a single, well-defined renal insult in the context of presumably normal preoperative renal function. Third, young age, higher risk-adjusted congenital heart severity (RACHS-1) score, and longer CPB time are well-described independent risk factors for acute renal failure.[22] Therefore, even though they had normal kidneys, this is a very high risk group with a high pretest probability of kidney injury. However, our study sample size was small and these results require reproducibility in larger studies across multiple centers before definitive conclusions can be reached.

We applied the Acute Kidney Injury Network criteria to classify patients into groups with and without acute renal injury. These criteria state that injury occurs if, within 48 hours of an insult, there is an absolute increase in serum creatinine of 0.3 mg/dL or more or by 50% over baseline, or if urine output is below 0.5 $mL \cdot kg^{-1} \cdot h^{-1}$ over a 6-hour period.[17] These criteria may lead to a bias toward classification of clinically significant renal injury, as exemplified by the fact that nearly 90% of placebo-treated patients in our series met criteria for acute kidney injury. Nonetheless, the application of these criteria makes clear the impressive renoprotective effect of NAC in this population. There are multiple other classification systems for acute kidney injury, including pediatric Risk, Injury, Failure, Loss, and End-Stage (pRIFLE)[23,24] and the Society of Thoracic Surgeons criteria. None of these systems has been shown to predict outcomes in a pediatric cardiac intensive care setting.

In addition to the small sample size, our study was limited because we did not measure glomerular filtration rate but instead used changes in serum creatinine, which may overestimate or underestimate the true glomerular filtration rate. By chance, 4 of the 5 patients who required aortic arch repair were randomized to the placebo group. This could have influenced the frequency of acute kidney injury, although a larger study would be required to show this. In addition, other biomarkers of renal injury that have recently been shown to correlate with outcomes after pediatric cardiac surgery, such as neutrophil gelatinase–associated lipocalin and cystatin C, were not analyzed.[25,26] Finally, NAC dosing was extrapolated from other clinical uses such as the treatment of acetaminophen intoxication. Given the lack of toxicity observed in this study, it is possible that a higher NAC dosing protocol could result in further renal protection.

The possibility that NAC, a seemingly safe and reasonably inexpensive agent, could result in significant cost savings for patients undergoing surgery for congenital heart disease based on reduced need for renal replacement therapy and shorter intensive care unit stays is an important finding of this study. Definitive conclusions await a randomized, placebo-controlled multicenter trial of NAC in neonates and young infants undergoing surgical repair for a variety of complex congenital heart lesions.

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